



Review Article

Nutritional Genomics and Microbiota to Control Postprandial Dysmetabolism

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Abstract

There is a causal relationship between cardiovascular risk and plasma levels of triglycerides, lipoproteins rich in triglycerides and remnants triglycerides. The importance of postprandial hyperlipidemia in the development of atherosclerosis was suggested by several studies. The mechanisms through which postprandial lipoproteins exert the atherogenic effect can be manifold. It has been hypothesized that the

postprandial phase corresponds to an inflammatory condition involving leukocytes and potentially contributing to endothelial dysfunction. In the pathogenesis of postprandial lipemia alterations, insulin resistance undoubtedly plays a leading role that is expressed at various levels. Obesity is associated with hypertriglyceridemia and low fasting HDL cholesterol levels. These abnormalities could

explain the high incidence of cardiovascular disease in the obese population. In recent years there has been a dramatic increase in diseases related to the alteration of metabolism, causing conditions such as obesity, type 2 diabetes (TD2), cardiovascular disease and metabolic syndrome (MetS). In addition to the numerous factors to which this increase has been attributed, such as diet, physical activity and inflammation, numerous studies provide evidence of a correlation between intestinal microbiota and metabolic diseases. The aim of this umbrella review is clarify the interactions between diet and lifestyle, microbes and health and therefore the relationship between gut microbiota and metabolic diseases so that one day we may perhaps know exactly how to direct our diet in order to be able to "shape" our microbiota to im-prove our health.

Key words: Metabolism; Obesity; Microbiota

1. Introduction

There is a causal relationship between cardiovascular risk and plasma levels of tri-glycerides, lipoproteins rich in triglycerides and remnants triglycerides. Lipoproteins rich in triglycerides and remnants accumulate in the plasma at TG values above 100 mg/dL and cardiovascular risk increases significantly for triglyceridemia greater than 150 mg/dL [1]. So the pathogenetic relationship between hypertriglyceridemia and cardio-vascular disease has been enough clarified thanks to the large amount of research carried out in recent decades but it has yet to be fully explained. One reason behind these difficulties is, first of all, the fact that the lipoproteins that transport triglycerides in the plasma (chylomicrons, very low density lipoproteins - VLDL - and their remnants, i.e. the particles that are formed by their catabolism) constitute a population very

heterogeneous in origin, structure and mode of interaction with cell receptors, so it is likely that they also have a different degree of atherogenicity [1]. But an even more important reason is certainly the fact that the plasma levels of lipids used to assess cardiovascular risk are measured in the fasting state and not in the postprandial phase, a condition in which, also considering today's conditions of well-being, we practically spend the 'all day. It should be considered that "postprandial lipemia" is a physiological process in which plasma lipoproteins and their subfractions undergo specific changes in concentration and composition following the intake of a meal, and in particular, a meal rich in fat. By "postprandial hyperlipidemia", on the other hand, we mean the quantitative, or even qualitative, alterations of this process. The clinical relevance of these lipoprotein alterations [2] lies in the important role they appear to play in the development of cardiovascular diseases. The aim of this umbrella review is clarify the interactions between diet and lifestyle, microbes and health and therefore the relationship between gut microbiota and metabolic diseases so that one day we may perhaps know exactly how to direct our diet in order to be able to "shape" our microbiota to improve our health.

2. Postprandial metabolism of lipoproteins

Most dietary fats are represented by triglycerides, which under normal conditions are almost completely absorbed in the small intestine, where pancreatic lipase splits the ester bond between fatty acids and glycerol. The intestinal lipid content is emulsified by bile salts and phospholipids and collected in water-soluble micelles which penetrate the enterocytes by diffusion. Glycerol and short-chain fatty acids (with less than 10-12 carbon atoms) then enter the bloodstream and are transported directly to the liver

via the portal vein while long-chain fatty acids are reesterified to triglycerides and introduced into the chylomicrons, which instead enter the bloodstream through the lymphatic one. The subsequent metabolic fate of triglycerides is determined by the protein component of the chylomicrons. Apolipoprotein (apo) B-48, synthesized in the intestine, is its structural component. Apo C-II, activator of lipoprotein lipase (LPL) and apo E, ligand of the receptor for chylomicron remnants, are transferred to them by plasma HDL (high density lipoprotein). LPL linked to the vascular endothelium of adipose tissue and muscle tissue mediates the hydrolysis of most of the triglycerides contained in the chylomicron core. In conjunction with this lipolysis, phospholipids and other surface molecules are transferred to the HDL, which donate cholesterol esters in exchange for

triglycerides. The remnants of the chylomicrons are then cleared from the circulation by receptor-mediated hepatic uptake. VLDL of hepatic origin contribute to the pool of postprandial plasma lipoproteins. Like chylomicrons, they undergo a reduction in their triglyceride content by the action of LPL and are then removed from the circulation by endocytosis mediated by the receptor that recognizes apo B-100 and apo E. A certain amount of VLDL, however, it is directly converted into intermediate (IDL) and low (LDL) density lipoproteins. Therefore, in the postprandial phase the particles of intestinal origin (chylomicrons and their remnants) and those of hepatic origin (different subfractions of VLDL) compete for the same enzymatic and receptor systems responsible for their catabolism [3].

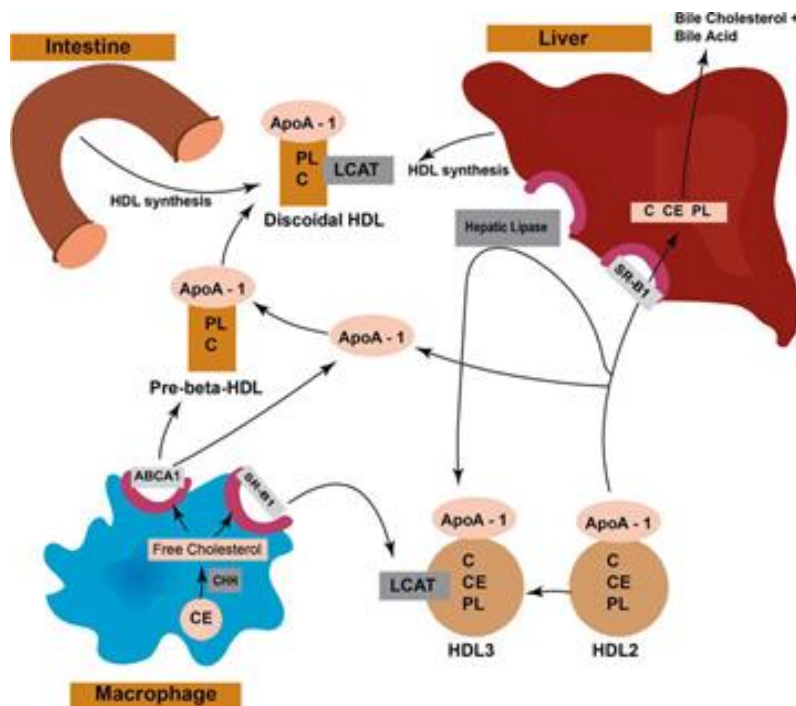


Figure 1: Lipoprotein metabolism (by Zhyvotovska, Yusupov, McFarlane, Introductory Chapter: Overview of Lipoprotein Metabolism, DOI: 10.5772/intechopen.85094).

2.1 Role of the apo E genotype on postprandial lipemia

There are different isoforms of apo E (E2, E3 and E4), which seem to have different binding properties and therefore affect the efficiency of the receptor-mediated uptake of the remnants of the chylomicrons. The genotype E2/E2, which is present only in 1% of the general population, but in 90% of patients with hyperlipidemia of type III, is associated with prolonged retention of chylomicron remnants compared to the more common E3/E33 genotype. However, it is still controversial whether the heterozygous E2 genotype is associated with a delay in the clearance of chylomicron remnants in normolipidemic subjects. Indeed, a reduced clearance in subjects with the E2/E3 genotype was observed in some studies in both healthy subjects [5-7] and in patients with type 2 diabetes mellitus [7] but not in other studies in healthy subjects [4,9-11] and in obese women [12]. Also for the E4 allele, which is associated with increased fasting total and LDL cholesterol levels and an increased cardiovascular risk [13,14], the data are conflicting regarding the independent effect on the postprandial lipemic response [5-6,10,15-16]. A preferential association of the E4 allele with lipoproteins rich in triglycerides (TRL) was found compared to HDL [17-18]. This different conformation of the apo E4 on the TRLs could produce a reduction in receptor binding compared to the apo E3 and therefore a lower uptake of VLDL with a consequent greater conversion of these lipoproteins into LDL [19]. It can be concluded that the apo E genotype is most likely an important factor in determining the postprandial lipemic response, but further studies are needed to clarify the relative weight of the different isoforms regardless of the basal values of plasma lipids and in different populations.

2.2 Methods of evaluation of postprandial lipemia

There are several methods for studying postprandial hyperlipemia [20]. The methodological objective is the precise characterization and quantification of lipoproteins rich in triglycerides that are formed in the postprandial period. The determination of plasma triglycerides after a meal is the simplest method, but it does not give information on the distribution in the different lipoproteins and does not allow to distinguish the exogenous particles from those of hepatic origin. Ultracentrifugation (UCF) allows lipoproteins to be separated based on their density and therefore based on their sedimentation constant (Sf). The different UCF techniques (analytical, preparative in solvent density and in density gradient, zonal etc.) allow the isolation, among the various classes of lipoproteins, of different subfractions in physico-chemical characteristics, but also in origin and fate metabolic. Many researchers have used the metabolic pathway of vitamin A on the basis that it is extensively incorporated into chylomicrons in the form of retinyl palmitate [21]. In human plasma, only a small amount of retinyl palmitate is exchanged with other lipoproteins, while, for the most part, it remains part of the chylomicrons until their hepatic uptake. Furthermore, vitamin A is excreted by the liver bound exclusively to retinol-binding proteins present in chylomicrons and is not incorporated into VLDL or LDL. Retinyl palmitate is therefore a specific marker for chylomicrons and their remnants, at least in the first part of the postprandial phase. The direct quantification of chylomicrons can be obtained through the determination of apo B-48 using an electrophoresis on sodium polyacrylamide dodecyl-sulfate gel which also allows its separation from particles containing apo B-100 by exploiting their different molecular weight [22]. It is a method subject to wide biological variability, but it is able to

give information on the number of circulating particles, as there is one apo B-48 particle for each chylomicronemic particle. Very recently, an enzyme immunoassay (ELISA) method has been proposed for the de-termination of apo B-48 which uses monoclonal antibodies directed against apo B-48 [23]. Data on its reliability are still missing. There are also immunological methods for the separation of remnants-like particles (RLP) from VLDL, which involve the use of immunoaffinity chromatography with monoclonal antibodies directed against an apo B-100 epitope, which is not present in the apo B-48, and which in addition to apo B-48 do not recognize a population of particles rich in triglycerides containing apo B-100 and rich in cholesterol esters and apoE [24]. In conclusion, the detailed assessment of postprandial lipemia, that is, the exact differentiation of the particles with regard to their lipid composition and their hepatic or intestinal origin, is difficult to perform as the methods currently available are complex and expensive. On the other hand, the simple determination of postprandial triglyceridemia, possible through the use, even at home, of portable reflectometers, can provide useful information for the identification and correction of the condition of postprandial hyperlipidemia [25-26].

2.3 Standardization of the test meal

Currently, very different meals are used for the study of dietary lipemia and this naturally makes it difficult to compare the results of different studies and makes it impossible to establish criteria for the normality of the lipemic response [27,28]. For a desirable standardization of the meal, several variables must be considered including mainly the type of nutrients to be included in the meal (fats/carbohydrates), the chemical composition of fats (saturated, monounsaturated, polyunsaturated), the caloric

content of the meal and the time of its intake, in addition to the environmental variables that are able to influence postprandial lipemia, such as smoking, exercise and alcohol intake [19,28]. A key element is the inclusion or not of nutrients other than lipids. In fact, meals composed only of fats or containing a variable proportion of carbohydrates were used, ranging from a load of cream to a mixed liquid meal or, more adherent to real life, solid. Of course, a meal made up of 100% fat, using for example cream as the only component, has the advantage of being simple to make and more reproducible and comparable in different situations and geographical areas than a mixed meal. On the other hand, it is too far from the usual diet as a "normal" meal completely devoid of carbohydrates is difficult to achieve. It is therefore impossible to build a standard meal that does not interfere with carbohydrate metabolism at all. In this regard, some studies suggest that sucrose, ingested with fat, increases postprandial triglyceridemia [29-31], unlike glucose which could even increase the clearance of chylomicrons probably due to the stimulation of insulin secretion. A high quantity of complex carbohydrates, on the other hand, has a fairly low acute lipogenic effect [32]. As for the protein content of the meal, it does not appear to influence postprandial triglyceridemia [33]. As regards the type of fats eaten with the meal, it must first of all be considered that dairy products contain a significant amount of short and medium chain fatty acids, which are absorbed as such and do not form chylomicrons, in addition to probably having an accelerated postprandial clearance [34-35]. Some studies [36,37], but not others [38,39], have found the formation of smaller chylomicrons with the intake of saturated fats than unsaturated ones. This could be due to methodological problems, as at 4°C (temperature at which plasma is generally treated) the

chylomicrons rich in saturated fatty acids tend to flocculate more easily since the core components move from the liquid to the crystalline phase [40]. This does not happen when the determination is carried out at 27°C. Vegetable oils, on the other hand, have a higher melting point and are therefore preferable from an analytical-methodological point of view. There is evidence that n-3 fatty acids, contained in fish oil, produce a lower triglyceride response than vegetable fatty acids and even more so in saturated ones [41-43]. In a study in healthy young people, a meal containing butter induced a higher response than one containing olive oil, with an increase in triglycerides concerning the fraction rich in chylomicrons and a greater and prolonged response of retinyl palmitate in this fraction [44]. However, it was reported in rats that clearance of chylomicrons containing a saturated fatty acid, palmitic, was faster than chylomicrons containing oleic or linoleic acid [41]. Overall, the fatty acid composition of the acute fat load does not appear to have a relevant effect on the lipemic response. With regard to the size of the meal, it must be taken into account that this should be such as to stimulate the metabolism without compromising absorption and gastric emptying times and, in any case, palatability. The optimal amount of fat in a meal should be between 50 and 80g [45,46]. A necessary condition for the execution of the meal is that this occurs fasting since the plasma levels of triglycerides before a fat load are a predictor of the postprandial lipemic response [47]. It would also be advisable to prohibit the intake of alcohol the day before the test as well as the execution of strenuous physical activity as it is able to modify the ability to remove circulating triglycerides [48]. In women, then, it is necessary to consider the possible intake of estrogen-based contraceptives as the latter seem to influence the

metabolism of chylomicron remnants [49]. In conclusion, there is currently no consensus on the type of meal to be used to stimulate the lipemic response. However, the clinical-diagnostic need which would require a less physiological meal, but more reproducible at an interpersonal and population level, must be distinguished from the clinical-prognostic need which in-stead can benefit from the detection of the lipemic response to the usual diet of a single individual.

2.4 Postprandial hyperlipidemia and cardiovascular diseases

The importance of postprandial hyperlipidemia in the development of atherosclerosis was suggested by the studies of Zilversmit, in which it was shown in animal models how the esterified cholesterol of the remnant of the chylomicrons accumulated in the anterior part of the aorta [50]. The evidence supporting the atherogenic effect of post-prandial plasma lipoproteins is numerous. These are mainly studies that have compared the postprandial lipemic response of patients with different clinical forms of atherosclerosis with that of control subjects without vasculopathy, by evaluating the degree of coronary obstruction [51-53] and the presence of peripheral arterial disease [54-56], but also of early indicators of vascular involvement such as carotid intimal thickness [57-59]. Already in the 1950s it was reported that coronary heart disease patients showed increased levels of plasma triglycerides for a prolongation of the postprandial condition [60]. A relationship with ischemic heart disease was then noted by Simons et al. [61] with an increased apo B-48/apo B-100 ratio in the postprandial phase and by Simpson et al. [62] with prolonged postprandial lipemia evaluated with retinyl palmitate. Patients with hypertriglyceridemic ischemic heart disease

have a slowed removal of chylomicrons from plasma [3]. Furthermore, the progression of the disease over a period of 5 years was related to the level of lipoprotein containing apo B-48 [63]. In a group of patients with severe coronary artery stenosis, age, postprandial plasma levels of triglycerides and fasting apo B were the best indicators of coronary risk [64]. Ginsberg et al. [65] also reported that myocardial ischaemia was associated with high postprandial plasma triglyceride levels regardless of other risk factors such as fasting LDL and HDL concentration. More recently it has been confirmed that the removal of chylomicron remnants from the circulation is slowed in both male [52] and female patients with normolipidemic ischemic heart disease [66,67]. It should be remembered that postmenopausal women, with or without ischemic heart disease, experienced a slowed removal of chylomicron remnants, so it is possible that estrogen deficiency is associated with impaired postprandial metabolism [68]. In conclusion, these studies indicate quite clearly that slow removal of chylomicrons from the remnant circulation is an independent risk factor for the development of atherosclerosis. At present, there are no prospective studies that have assessed the incidence of cardiovascular events in relation to the presence or absence of postprandial lipemia alterations. There are also no intervention studies on the effect of correcting postprandial lipemia on cardiovascular disease.

2.5 Possible atherogenic mechanisms

The mechanisms through which postprandial lipoproteins exert the atherogenic effect can be manifold. The remnants of lipoproteins rich in triglycerides could act directly in an atherogenic sense. In fact, they have been detected in human atherosclerotic plaques [69] and can promote an

inflammatory response in the arterial wall [70]. Remnants could also act by intervening in the coagulation processes, as it has been observed that they promote the activation of factor VII, an enzyme important in the production of thrombin, which in turn converts fibrinogen to fibrin in clot formation [71,72]. The activation of platelets and monocytes is a process potentially involved in the development of cardiovascular disease which appears to be associated with postprandial lipemia. In fact, after a moderately high-fat meal (40%) there was a significant increase in platelets expressing P-selectin on the surface and increased activation of the GP IIIb-IIa receptor, as well as an increase in platelet-monocyte aggregates and percentage of monocytes expressing TN- α and IL-1 beta [73].

2.6 Endothelial dysfunction

It has been hypothesized that the postprandial phase corresponds to an inflammatory condition involving leukocytes and potentially contributing to endothelial dysfunction. In fact, an increase in the blood of neutrophils, IL-8 and hydroperoxides in association with a reduction in flow-mediated vasodilation was observed in a group of healthy males during postprandial lipemia [74]. It also appears that a substantial increase in postprandial hyperlipidemia is associated with a reduction in endothelium-mediated vasodilation in the brachial artery [75-77]. This functional and structural marker of early atherosclerosis correlates proportionally to the degree of postprandial hyperlipidemia as it is related to the reduction of HDL, with antioxidant potential, and the increase of small and dense LDL which, on the contrary, oxidize easily [78-81]. Evans et al. [82] also observed that postprandial deterioration of endothelial function correlated directly with triglyceride levels in VLDL and LDL and inversely

with HDL cholesterol. In this study, in the postprandial phase, the triglyceride enrichment of VLDL was the only parameter correlated with oxidative stress evaluated as the level of free radicals. In conclusion, there is evidence that postprandial lipemia alters the function of the endothelium predisposing it to vasoconstriction and causing a proinflammatory and procoagulant state in various physiological and pathophysiological conditions. It would be interesting to link these activities with the development of atherosclerosis and/ or the triggering of acute coronary syndromes, but the evidence is still contradictory [83].

2.7 Postprandial hyperlipidemia and insulin resistance

In the pathogenesis of postprandial lipemia alterations, insulin resistance undoubtedly plays a leading role that is expressed at various levels. First of all, the altered sensitivity of the adipose and hepatic tissue to the action of insulin causes the normal suppression of the release of free fatty acids in the first and the production of VLDL in the second is altered. This implies that in the postprandial state the chylomicrons of intestinal origin and the hepatic VLDLs produced in excess compete for the common disposal mechanism that involves both the action of the LPL and the receptor-mediated uptake. In this regard, there are data that show, in the course of insulin resistance, a reduction in the expression of lipoprotein lipase in adipose tissue and an increase in the concentration of hepatic lipase [84]. Despite such evidence, the role of lipolytic enzymes in the pathogenesis of postprandial lipemia remains controversial [85]. Since insulin resistance is the common denominator of the various metabolic abnormalities that make up the metabolic syndrome, it contributes significantly to the genesis of

postprandial lipid alterations present in these conditions [86].

2.8 Type 2 diabetes mellitus

Postprandial hyperlipidemia, understood as the high persistence in the circulation of chylomicrons, VLDLs and their remnants, is an element characterizing the dyslipidemia of patients with type 2 diabetes [86-88]. The postprandial triglyceride peak is delayed (4-6 hours) and this means that, due to the succession of meals and the progressive accumulation, diabetic patients have high concentrations of triglycerides throughout the day, as has been found in studies in which the profile daily triglyceridemia was determined in patients with type 2 diabetes using a portable device [24]. The abnormalities of postprandial metabolism observed in type 2 diabetes consist of a prolonged stay in the circulation of both intestinal and hepatic origin particles, especially the remnants of these particles. These alterations have been found in diabetic patients with fasting hypertriglyceridemia. even if only moderate, and / or unsatisfactory glycometabolic compensation, while the observations are more disagree with regard to diabetic patients without fasting hypertriglyceridemia and in excellent glycometabolic compensation [89-92]. However, Rivelles et al.[93] have shown that even subjects with type 2 diabetes, fasting normotriglyceridemics and with optimal glycemic compensation have alterations in postprandial lipoproteins affecting both exogenous and endogenous lipo-proteins. There are numerous evidences supporting the relationship between insulin resistance, which is a fundamental element in the pathogenesis of type 2 diabetes, and the alterations of postprandial lipid metabolism. Jeppesen et al. [94] have, in fact, observed that in healthy non-diabetic individuals, insulin-mediated

resistance to the use of glucose was an independent factor associated with lipid alterations in the postprandial phase. Axelsen et al. [95] also reported an increase in the postprandial incremental area of triglycerides after a standard mixed meal in first-degree relatives of type 2 diabetic patients, who presented insulin resistance, but were normoglycemic and normotriglyceridemic. Annuzzi et al. [96] experimentally demonstrated for the first time the specific role of insulin resistance in type 2 diabetic patients in the absence of the confounding factors represented by hyperglycemia and hyperinsulinemia, which are characteristic of these patients. In fact, their lipemic response to a high-fat meal during a hyperinsulinemic glycemic clamp, compared with that of non-diabetic control subjects, was altered due to a postprandial increase in lipoproteins rich in triglycerides of both exogenous and endogenous origin. The fact that this has been observed in patients with excellent glycemic control and optimal fasting triglyceride values is clinically relevant, as it suggests that these postprandial changes are even more evident in patients with glycemic metabolic decompensation.

2.9 Obesity

Obesity is associated with hypertriglyceridemia and low fasting HDL cholesterol levels. These abnormalities could explain the high incidence of cardiovascular disease in the obese population. However, obesity appears to be an independent risk factor for coronary heart disease even in subjects with normal fasting plasma lipid levels and glucose tolerance. Android-type obesity patients with normal fasting triglyceride levels and no different from those of healthy controls show an abnormal postprandial response of plasma lipids, indicated by an increase in triglycerides in non-chylomicronemic subfractions,

significantly higher than in healthy controls [96]. These alterations could be due, in particular, to the modifications of the endogenous lipoproteins consequent to the insulin resistance. In particular, a study by Couillard et al. [97] investigated the relationship between postprandial lipemia, fasting triglyceridemia, and visceral accumulation of adipose tissue. The results of this study suggested that the increase in lipolysis at the level of visceral adipocytes, due to the state of insulin resistance related to obesity, determines an increase in plasma levels of triglycerides and VLDL for the hepatic reesterification of high levels of non-esterified fatty acids released into the portal circulation.

2.10 Hypertension

A study by Kolovou et al. [98] examined the relationship between hypertension and postprandial hyperlipidemia by comparing the response to a high-fat meal of a group of 25 hypertensive patients with that of 25 healthy subjects. The results of this study indicated that hypertension, regardless of other conditions of the metabolic syndrome, is associated with an excessive postprandial peak and delayed clearance of plasma triglycerides.

2.11 Other conditions associated with insulin resistance

Recent data have highlighted the existence of a relationship between insulin resistance syndrome and cigarette smoking [99]. It has been shown that some aspects of the insulin resistance syndrome such as hyperinsulinemia, high levels of hypertriglyceridemia, reduced HDL-cholesterol levels and dysfibrinolysis are related to the daily consumption of nicotine. Axelsen et al. [100] observed that smokers also seem to have an impaired elimination of

triglycerides after the intake of a high-fat meal regardless of fasting triglyceride values.

2.12 Treatment of postprandial hyperlipidemia

2.12.1 Diet: Studies in humans and animals have shown that the fatty acid composition of the usual diet can influence the extent and duration of postprandial lipemia. First of all, as already discussed, fatty acids a medium and short chain are not incorporated in the chylomicrons so there is less postprandial increase triglyceridemia when more medium- and short-chain fatty acids are used than those of the chain long. It has been observed that polyunsaturated fatty acids of the ω 3 type are able to reduce the concentration of chylomicrons and their remnants, probably as a result of a reduced production of VLDL and therefore less competition for the lipolysis of these particles in the postprandial phase [101,102]. On the contrary, there is evidence of a higher and prolonged postprandial lipemic response in the presence of an increased dietary intake of saturated fatty acids compared to polyunsaturated ones and this seems to be due to an increased secretion of VLDL [103,104]. As regards the influence of the dietary intake of cholesterol, it was reported that no differences were observed in postprandial lipemia if the diet contained 0 to 4 eggs per day [105]. In this study, however, healthy young subjects were evaluated for which the effect may be different in patients with cardiovascular risk factors and, more-over, it must be remembered that the effects of dietary cholesterol are dependent on the fatty acid composition of the diet. It has been shown that the cholesterol esters contained in chylomicrons (and probably also free cholesterol) derive from endogenous sources and that only a limited quantity is of food origin [106], even if 50% of the cholesterol taken from the diet is still absorbed and can not only

be transported by the large chylomicrons that are secreted by the intestine immediately after a meal, but also by small chylomicrons produced continuously in the post-absorbing state [107]. With regard to the other components of the diet, it should be remembered that carbohydrates, if chronically consumed in excessive quantities (especially if it is sucrose and fructose), can induce an excessive formation of VLDL by the liver and therefore hypertriglyceridemia [108]. In these conditions, the postprandial lipemic response is increased [109], particularly in patients with diabetes mellitus type 2 [110]. Dietary fibers, with a well-documented cholesterol-lowering effect, which has been attributed to intraluminal sequestration of cholesterol, appear to have a limited effect on postprandial triglycerides [111-113]. Acute and chronic alcohol intake is associated with a slowdown in the removal of postprandial triglycerides [114] and the effect seems to be more evident if the meal contains saturated fatty acids [115].

2.12.2 Physical activity: Several studies indicate that a training period reduces postprandial lipemia [116-119]. There is evidence that even a single session of exercise is able to improve the postprandial lipemic response [120] and that the effects are only observed up to three days after the end of a training period [121] and could therefore be the result of the last training session [48]. This therefore implies that, in order to maintain the benefits in terms of reducing the presence of postprandial atherogenic particles in the circulation, physical exercise, in line with the recommendations proposed for improving cardiovascular risk, must be conducted regularly and frequently.

2.12.3 Pharmacological therapy: Lipid-lowering drugs. The drugs commonly used to treat hyperlipidemias seem to be able to reduce the concentration of lipoproteins rich in triglycerides and their remnants present in the postprandial phase. Several studies have evaluated the effects of fibrates. In a study in type 2 diabetic patients with moderate hypertriglyceridemia, gemfibrozil reduced the concentration of the largest postprandial lipoproteins (Sf > 400), of almost exclusively intestinal origin [122]. In this study, the largest VLDLs (Sf 60-400) also decreased with a reduction in retinyl palmitate in this fraction, demonstrating the effect of chylomicrons on remnants. Similar results were obtained with gemfibrozil in hyper-lipidemic patients [123], while a reduction in the triglyceride concentration in the post-prandial fraction $d < 1006$ was observed with fenofibrate, but not in the levels of retinyl palmitate [62]. Attia et al. [124] observed a reduction in triglycerides in fractions with Sf > 400, 12-400 and <12 both fasting and after a predominantly lipid meal in moderately hyperlipidemic diabetic patients treated for four weeks with bezafibrate. The hypothesized mechanism underlying these results would be the ability of the fibrates to reduce the levels of triglycerides of endogenous origin with a consequent lower competition between particles of endogenous and exogenous origin at the level of receptor-mediated hepatic removal. Treatment with bezafibrate also appears to be able to restore normal cholesterol efflux levels from both fasting and postprandial cells by improving the reverse transport of cholesterol, the latter mechanism which in insulin-resistant patients is altered due to slowing postprandial lipolysis of lipoproteins rich in triglycerides [125]. Other mechanisms on which fibrates could act are increased oxidative stress and endothelial dysfunction,

phenomena which, as already discussed, are observed during the postprandial phase. In fact, in a controlled study in 20 diabetic patients, treatment for three months with ciprofibrate resulted in the reduction of fasting plasma triglycerides and their incremental postprandial area, as well as an increase in HDL cholesterol levels. And these effects were closely correlated with the improved endothelial function and reduction of oxidative stress observed in the postprandial phase [126]. Several studies have evaluated the effects of statins on postprandial lipemia. In patients with type 2 diabetes in stable glycemic control and combined hyperlipidaemia, treatment with simvastatin induced not only a reduction in total and LDL cholesterol levels and an increase in fasting HDL cholesterol, but also a reduction in postprandial triglycerides [127]. Atorvastatin was also effective compared to placebo in reducing postprandial triglyceridaemia in a group of patients with impaired fasting glucose [128]. In a study in patients with mixed hyperlipidaemia, the beneficial effects of atorvastatin on postprandial lipemic profile and cardiovascular risk were enhanced by the addition of a low dose of omega-3 fatty acids, which produced a further significant increase in cholesterol levels. HDL and decrease in small and dense LDL concentration and postprandial triglyceridemia [129]. The association atorvastatin-omega-3 fatty acids was also found to be able to reduce the activation of coagulation in the course of postprandial lipemia, reducing the concentration of activated factor VII, its coagulant activity and the FVII antigen [129]. Some studies have compared the postprandial effects of statins with those of fibrates. In a study that compared gemfibrozil and lovastatin in patients with hypoalphalipoproteinemia and mild/moderate hypertriglyceridemia, the reduction in fasting triglyceridemia was related to the

improvement in postprandial lipemia, probably thanks to the increase in LPL mediated lipolysis [130]. Gemfibrozil was more effective than lovastatin in reducing postprandial lipemia [131]. Wilmink et al. [132] compared the effects of cerivastatin and gemfibrozil on changes in endothelial function induced by a high-fat meal. Cerivastatin but not gemfibrozil was able to significantly improve postprandial endothelial dysfunction in direct proportion to the effect on lipoproteins, suggesting that lowering remnant cholesterol rather than lowering total triglyceride levels may contribute to the prevention of endothelial dysfunction. postprandial. Statins are the treatment of choice for lowering LDL cholesterol because they have proven efficacy in reducing cardiovascular morbidity and mortality. Statins inhibit hydroxymethylglutaryl-CoA reductase, a key enzyme in the synthesis of cholesterol, leading to positive regulation of LDL receptors and increased LDL clearance. They reduce LDL cholesterol by up to 60% and cause small increases in HDL and a modest reduction in triglycerides. Additionally, statins appear to reduce intra-arterial inflammation and systemic inflammation, or both, by stimulating endothelial nitric oxide production and may have other beneficial effects. Other classes of lipid-lowering drugs are not the first choice, because they have not demonstrated equivalent efficacy for reducing atherosclerotic cardiovascular disease [134]. Statin treatment is classified as high, moderate or low intensity and is given based on treatment group and age. Statin choice may depend on patient comorbidities, other medications, risk factors for adverse events, statin intolerance, cost and patient preference. Adverse effects with statins are rare but include elevated liver enzymes and myositis or rhabdomyolysis. Elevations in liver enzymes are rare, and severe liver toxicity is

extremely rare. Muscle problems occur in 10% of statin-treated patients and can be dose-dependent. Muscle symptoms can occur without enzyme elevation. Adverse effects are more frequent in elderly patients, in patients with several comorbidities and in those taking numerous drug therapies. In some patients, changing the statin type or reducing the dose (after temporarily stopping the drug) solves the problem. Muscle toxicity appears to be more common if some of the statins are used in combination with drugs that inhibit cytochrome P3A4 (eg, macrolide antibiotics,azole antifungals, cyclosporine) and with fibrates, especially gemfibrozil. Statins are contraindicated during pregnancy and breastfeeding. In patients with atherosclerotic cardiovascular disease, the greater the reduction in LDL cholesterol achieved by statin therapy, the greater the reduction in risk. Thus, the initial treatment is a statin at the maximum tolerated dose to reduce LDL cholesterol > 50% (high intensity therapy). Despite maximal statin therapy, patients with very high-risk atherosclerotic cardiovascular disease (eg, those with recent myocardial infarction or unstable angina, or with high-risk comorbidities such as diabetes) and LDL cholesterol values > 70 mg / dL (> 1.2 mmol / L) should be added to therapy with ezetimibe or a PCSK9 inhibitor (eg, evolocumab, alirocumab). With the advent of combination therapy using ezetimibe and/or proprotein convertase subtilisin/kexin type 9 inhibitors in addition to statins, the routine attainment of extremely low LDL-C levels in the clinic has become a reality [133]. In large clinical trials [134,135], these therapies in combination with statin therapy have been shown to reduce major cardiovascular adverse events. Bile acid sequestering drugs block intestinal reabsorption of bile acids, resulting in the positive regulation of hepatic LDL

receptors, in order to find circulating cholesterol for the synthesis of bile. They are promising to reducing cardiovascular mortality. Bile acid sequestrants are usually used in conjunction with statins or nicotinic acid to enhance the LDL cholesterol-lowering effect and are the drugs of choice for pregnant or maternity-planning women. Bile acid sequestrants are safe, but their use is limited by the adverse effects of bloating, nausea, cramping pain and constipation. They can also increase triglyceride levels and therefore their use is contraindicated in patients with hypertriglyceridemia. Cholestyramine, colestipol and colesevelam (but to a lesser extent) interfere with the absorption of other drugs, especially thiazides, beta-blockers, warfarin, digoxin, and thyroxine, an effect that can be minimized by administration at least 4 h before or 1 h after other drugs. Drugs that sequester bile acids must be given with meals to increase their effectiveness. Cholesterol absorption inhibitors, such as ezetimibe, inhibit the intestinal absorption of cholesterol and phytosterols. Usually ezetimibe lowers LDL cholesterol by 15-20% and causes a small increase in HDL and a slight decrease in triglycerides. Ezetimibe can be used as monotherapy in statin intolerant patients or added to statins in patients with persistently elevated LDL cholesterol despite taking a maximal statin dosage. Adverse effects are rare. PCSK9 monoclonal antibodies are available as subcutaneous injections administered once or twice a month. These drugs prevent PCSK9 from binding to LDL receptors, resulting in improved function of these receptors. LDL cholesterol is lowered by 40 to 70%. A cardiovascular outcome test with evolocumab and alirocumab showed a reduction in cardiovascular events in patients at high risk for atherosclerotic cardiovascular disease [134]. Dietary supplements that lower LDL cholesterol levels include fiber supplements and commercially

available margarines and other products that contain plant sterols (sitosterol, campesterol) or stanols. Fiber-based supplements reduce cholesterol levels in multiple ways, including reduced absorption and increased excretion. Oat fiber supplements can reduce total cholesterol by up to 18%. Plant sterols and stanols decrease cholesterol absorption by replacing cholesterol from intestinal micelles and can reduce LDL cholesterol by up to 10% without affecting HDL or triglycerides. Medicines for homozygous familial hypercholesterolaemia include mipomersen and lomitapide. Mipomersen is an apo B antisense oligonucleotide that decreases the synthesis of apo B in liver cells and decreases the levels of LDL, apo B, and Lp(a). It is given by subcutaneous injection and can cause injection site reactions, flu-like symptoms, increased liver fat and elevated liver enzymes. Lomitapide is a microsomal triglyceride transfer protein inhibitor that interferes with the secretion of triglyceride-rich lipoproteins in the liver and intestines. The dose was started at a low dose and gradually titrated up about every 2 weeks. Patients should be on a diet with less than 20% calories from fat. Lomitapide can cause gastrointestinal adverse effects (eg, diarrhea, increased hepatic steatosis, elevated liver enzymes). Procedural approaches are reserved for patients with severe hyperlipidemia (LDL cholesterol > 300 mg / dL [> 7.74 mmol / L]) and no vascular disease. LDL apheresis can be performed on patients with LDL cholesterol > 200 mg / dL (> 5.16 mmol / L) and vascular disease refractory to conventional therapy, as occurs in familial hyper-cholesterolemia. Options are extracorporeal LDL apheresis (in which LDL is removed by plasmapheresis [plasma exchanges]) and, rarely, ileal bypass (to block the reabsorption of bile acids) and liver transplantation (which also transplants the receptors for LDL). LDL apheresis is

the procedure of choice in most cases when maximum tolerated therapy does not adequately reduce LDL. Apheresis is also the usual therapy in patients with the homozygous form of familial hypercholesterolemia, which has little or no response to drug therapy. Fibrates reduce triglycerides by about 50%. They appear to stimulate endothelial lipoprotein lipase, leading to increased oxidation of fatty acids in the liver and muscles and reduced hepatic synthesis of VLDL. They also increase HDL by up to 20%. Fibrates can cause adverse effects on the gastrointestinal tract, such as dyspepsia, abdominal pain and elevated liver enzymes. They rarely cause cholelithiasis. Fibrates can potentiate muscle toxicity when used in combination with statins and enhance the effect of warfarin. Statins can be used in patients with triglycerides <500 mg / dL (<5.65 mmol / L) if elevated LDL cholesterol levels are also present; statins can reduce both LDL cholesterol and triglycerides by reducing VLDL. If only triglycerides are elevated, fibrates are the drugs of choice. High-dose omega-3 fatty acids (1-6 g / day of eicosapentaenoic acid and docosahexaenoic acid) can be effective in lowering triglycerides. The omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid are the active ingredients in fish oil or omega-3 capsules. Adverse effects include belching and diarrhea. These effects can be reduced by giving the fish oil capsules during meals in divided doses (eg, 2 or 3 times / day). Omega-3 fatty acids can be helpful in addition to other therapies. Prescription omega-3 fatty acids are indicated for triglyceride levels > 500 mg / dL (> 5.65 mmol / L). The Apo CIII inhibitor (an antisense inhibitor of apo CIII), volanesorsen, is currently available in some countries. Lowers triglyceride levels in patients with severely elevated triglyceride levels, including patients with lipoprotein lipase deficiency. It is given

as a weekly injection [136]. Hypoglycemic drugs. Metformin by virtue of its insulin-sensitizing properties in the different types of tissues proved effective in improving postprandial lipemia both in patients with type 2 diabetes in poor glycemic compensation only with sulfonylureas [136], and in non-diabetic subjects but with impaired glucose tolerance [136]. In both studies, treatment with metformin, in addition to reducing the area under the postprandial glucose and insulin curve, reduced the postprandial area of retinyl-palmitate in chylomicrons (56%) and in the non-chylomicronemic fraction (32%). As for insulinotropic drugs, however, a study in type 2 diabetic patients in good glycemic control did not show any effect on postprandial lipemia of either glibenclamide or nateglinide [137-139]. Sulfonylureas are insulin secretagogues. They lower blood glucose by promoting insulin secretion by pancreatic beta cells and may secondarily improve peripheral and hepatic sensitivity to insulin, reducing glucose toxicity. First generation drugs (see table Some Combinations of Oral Hypoglycemic Drugs by Class) cause adverse effects more frequently and are rarely used. All sulfonylureas promote hyperinsulinemia and a weight gain of 2-5 kg which, over time, can enhance insulin resistance and limit their usefulness. All of them can also cause hypoglycemia. Risk factors include age > 65, use of long-acting drugs (especially chlorpropamide, glyburide, or glipizide), improperly planned diet and exercise, and kidney or liver failure. Hypoglycemia caused by long-acting drugs can last for days after stopping treatment, can sometimes cause permanent neurological damage and can be fatal. For these reasons, some doctors prefer to hospitalize people with hypoglycemia, particularly the elderly. Chlorpropamide can also cause the syndrome of inappropriate antidiuretic hormone secretion.

Ultimately, most patients on sulphonylurea alone require additional medications to maintain euglycemia, indicating that the sulphonylureas may deplete beta cell function. However, worsening of insulin secretion and insulin resistance is probably more a feature of diabetes mellitus itself than of the drugs used to treat it. Fast-acting insulin secretagogues (repaglinide, nateglinide) stimulate insulin secretion in a similar way to sulphonylureas. However, they have a faster action and can stimulate insulin secretion more during meals than at other times. They are therefore particularly effective in reducing postprandial hyperglycemia and appear to lead to a lower risk of hypoglycemia. There may be some weight gain, although evidently less than with sulphonylureas. Patients who have not responded to oral hypoglycemic agents of other classes (eg, sulphonylureas, metformin) are unlikely to respond to these drugs. Biguanides reduce blood sugar by lowering hepatic production of glucose (gluconeogenesis and glycogenolysis). They are considered peripheral insulin sensitizers, but their stimulation on peripheral glucose uptake may simply be the result of their hepatic effects. Biguanides also reduce lipid levels and can reduce the absorption of nutrients from the gastrointestinal tract, increase the sensitivity of beta cells to circulating glucose, and reduce the levels of plasminogen activator inhibitor 1, thus having an antithrombotic effect. Metformin is the only commercial biguanide in the United States. It is at least as effective as sulphonylureas in lowering blood sugar, rarely causes hypoglycemia, and can be used safely in combination with other drugs and insulin. Additionally, metformin does not cause weight gain and may also promote weight loss by reducing appetite. However, the drug typically causes gastrointestinal adverse effects (eg, dyspepsia, diarrhea) that, in most people, resolve over time. Less

commonly, metformin causes vitamin B12 malabsorption, but clinically significant anemia is rare. The contribution of metformin to the development of life-threatening lactic acidosis is very rare, but the drug is contraindicated in patients at risk of acidosis (including those with significant renal insufficiency, heart failure, hypoxia or severe respiratory disease, alcoholism, other forms of metabolic acidosis or dehydration). The drug should be discontinued during surgery, IV administration of contrast media and any serious illness. Many people treated with metformin alone eventually require the addition of an additional drug. Thiazolidinediones decrease peripheral insulin resistance (insulin sensitizers), but their specific mechanism of action is not fully understood. These drugs bind a nuclear receptor present mainly in fat cells (peroxisome-proliferator-activated receptor- γ [PPAR- γ]), which is involved in the transcription of genes that regulate glucose and lipid metabolism. Furthermore, thiazolidinediones increase HDL levels, reduce triglycerides and can have anti-inflammatory and anti-atherosclerotic effects. Thiazolidinediones are as effective as sulphonylureas and metformin in reducing HbA1C. Thiazolidinediones may be useful in the treatment of nonalcoholic fatty liver disease (NAFLD). Although a thiazolidinedione (troglitazone) caused acute liver failure, currently marketed drugs have shown no hepatotoxicity. Nonetheless, periodic monitoring of liver function is recommended. Thiazolidinediones can cause peripheral edema, especially in patients taking insulin, and can worsen heart failure in predisposed patients. Weight gain, due to fluid retention and an increase in fat mass, is common and may be relevant (> 10 kg) in some patients. Rosiglitazone may increase the risk of heart failure, angina, myocardial infarction, stroke, and fractures. Pioglitazone may

increase the risk of bladder cancer (although the data are conflicting), heart failure and fractures. Alpha-glucosidase inhibitors competitively inhibit intestinal enzymes that hydrolyze dietary carbohydrates; carbohydrates are digested and absorbed more slowly, thus reducing postprandial blood sugar. Alpha-glucosidase inhibitors are less effective than other oral drugs in lowering blood glucose and often cause dyspepsia, flatulence, and diarrhea, causing patients to discontinue therapy. Aside from that, these are otherwise safe drugs that can be used in combination with all other oral hypoglycemic agents and with insulin. Dipeptidyl peptidase-4 inhibitors (eg, alogliptin, linagliptin, saxagliptin, sitagliptin) prolong the action of endogenous glucagon-like peptide-1 (GLP-1) via inhibition of the implicated dipeptidyl peptidase-4 enzyme in the decomposition of GLP-1. There is a slightly increased risk of pancreatitis with dipeptidyl peptidase-4 inhibitors, but they are otherwise considered safe and well tolerated. The decrease in HbA1C is modest with dipeptidyl peptidase-4 inhibitors. Sodium glucose cotransporter type 2 inhibitors (canagliflozin, dapagliflozine, empagliflozine) inhibit the sodium glucose cotransporter type 2 in the proximal tubule of the kidney, which blocks glucose reabsorption causing glycosuria, and lowering plasma glucose. Sodium-glucose co-transporter type 2 inhibitors can also cause modest weight loss and lower blood pressure. Empagliflozin has been shown to reduce cardiovascular events in diabetic patients at high risk for cardiovascular disease. The most frequent side effects are genitourinary infections, in particular fungal infections. Orthostatic symptoms may also appear. There have been reports of diabetic ketoacidosis in patients with type 1 diabetes mellitus and type 2 diabetes mellitus. Bromocriptine is a dopamine agonist that lowers HbA1C by

approximately 0.5% by an unknown mechanism. Although approved for type 2 diabetes mellitus, it is not commonly used due to the potential negative effects. Injectable hypoglycemic drugs other than insulin are glucagon-like peptide 1 receptor agonists [GLP-1] and the amylin analogue, pramlintide (see table Characteristics of non-insulin injectable hypoglycemic drugs). These drugs are used in combination with other hypoglycemic agents. GLP-1 agonists (exenatide [a hormone that stimulates secretion], liraglutide, dulaglutide, albiglutide) increase glucose-dependent insulin secretion and slow gastric emptying. GLP-1 agonists can also reduce appetite, promote weight loss, and stimulate beta cell proliferation. Formulations are available for dosing twice / day, once / day and weekly. The most common adverse effects of GLP-1 agonists are gastrointestinal, in particular nausea and vomiting. GLP-1 agonists also cause a slightly increased risk of pancreatitis. They are contraindicated in patients with a personal or family history of medullary thyroid carcinoma because an increased risk of this tumor has occurred in experiments with animal models. The amylin analog pramlintide mimics amylin, a pancreatic hormone produced by beta cells that helps regulate postprandial blood sugar. Pramlintide suppresses postprandial glucagon secretion, slows gastric emptying, and promotes satiety. It is given by injection and is used in combination with insulin given during meals. Patients with type 1 diabetes mellitus are given 30-60 mcg subcutaneously before meals, those with type 2 diabetes mellitus are given 120 mcg [137-139].

2.13 Relationship between intestinal microbiota and metabolic diseases

In recent years there has been a dramatic increase in diseases related to the alteration of metabolism,

causing conditions such as obesity, type 2 diabetes (TD2), cardiovascular disease and metabolic syndrome (MetS). In addition to the numerous factors to which this increase has been attributed, such as diet, physical activity and inflammation, numerous studies provide evidence of a correlation between intestinal microbiota and metabolic diseases. Over the past decade, the body of published studies providing evidence on the relationship between gut microbiota and metabolic diseases has soared compared to twenty years ago. The ability to understand as microbiota be able to modulate it could represent the new frontier for the prevention and treatment of major metabolic diseases such as type 1 diabetes, type 2 diabetes, metabolic syndrome and obesity.

2.14 Microbiota and metabolism

The microbiota plays an important role in many metabolic functions, including the modulation of blood sugar and lipid homeostasis, the regulation of satiety, the production of energy and vitamins. It plays a role in the regulation of numerous biochemical and physiological mechanisms through the production of metabolites and substances. In addition, the microbiota also carries out important anti-inflammatory actions. There is growing evidence that changes in the composition of the microbiota can lead to various diseases, including metabolic diseases, such as obesity and diabetes, and cardiovascular disease. It is interesting to underline how the current and future preventive and therapeutic strategies to prevent these diseases definitely focus on adequate modulation of the microbiota [1].

2.15 The human microbiota

The microbiota is a complex ecosystem of microorganisms made up of bacteria, vi-ruses,

protozoa, fungi and archea, which live in different areas of the human body, such as the gastrointestinal tract, skin, mouth, respiratory system and vagina. Over 70% of microbiota lives in the gastrointestinal tract in a mutually beneficial relationship with its host. The qualitative and quantitative composition of microorganisms varies in the different sections of the digestive system. In particular at the gastric level it is possible to isolate a concentration equal to about 10³ CFU/ml. This concentration progressively increases in the small intestine up to about 10²-10⁹ CFU/ml and in the large intestine up to about 10⁴-10¹² CFU/ml. These bacterial species mainly belong to the Firmicutes and Bac-teroidetes phyla, both deriving from a common precursor: *Methanobrevibacter smithii*. In an individual weighing 70kg, the human gut microbiota gathers more than 100 trillion microorganisms and weighs about 200g (equivalent to a medium-sized mango) [140-142]. It is possible to say that "the human intestinal microbiota has a metabolic activity equal to an organ in the organ" and through this activity it performs certain beneficial functions for the host, such as production of essential metabolites, formation of fecal mass and intestinal gas, immune modulation also including antibiotic activity, xenobiotic degradation, and metabolic function affecting the digestion and absorption of nutrients. Backhed et al. [143], in 2004, stated that the microbiota can be considered as a metabolic organ exquisitely converted to our physiology that performs functions that we are unable to perform otherwise. These functions include the ability to assimilate otherwise indigestible components of our diet, such as plant polysaccharides. The microbiota is influenced by nutrition, lifestyle, exercise, use of antibiotics and genetics. It is involved in the regulation of the production of short-chain fatty acids (SCFA), basic in

the regulation of food absorption and insulin modulation in the generation of a low degree of inflammation. Colonization of the intestine begins even before childbirth and the first three years of life seem essential for the development of the immune system. The imbalance of the intestinal microbiota leads to the so-called "intestinal dysbiosis" which seems to be involved in the development of the major immune-mediated diseases. The mode of delivery can also determine the microbiota of the unborn child. Babies born with spontaneous delivery take up part of the vaginal microbiota while babies born via caesarean section have a different imprinting with less microbiota diversification. Furthermore, premature babies have a microbiota characterized by poor diversity, instability and delayed maturation. Finally, breastfeeding also affects the development of the microbiota in a different way than breastfeeding with humanized milks. Human milk oligosaccharides (HMOs) are considered to be able to act as growth

factors for beneficial intestinal bacteria in the infant. The intestinal microbiota has a great resilience and therefore tends to return to the starting conditions after the end of the disturbing event. Therefore, to modulate our microbiota we have to think about very long interventions to avoid a rapid return to the initial dysbiosis. In other words, antibiotics can induce changes in the microbiota even in the long term. The main environmental factor for the modulation of the microbiota is perhaps nutrition [144]. Undigested or incompletely digested carbohydrates are important food substrates for the microbiota. For example, we find among these, complex starches and dietary fibers, such as cellulose and hemicellulose, which includes xylans, such as bran, glucomannans, and pectins. Lipids, on the other hand, cannot be used by intestinal anaerobic bacteria, as the oxidation of long-chain fatty acids requires the presence of oxygen, which is poor in intestine.



Figure 2: The intestinal microbiota (by <https://www.thesautonapproach.it/microbiota-intestinale-come-prendersene-cura/>).

2.16 Microbiota and type 2 diabetes mellitus

Some studies have examined whether an altered intestinal microbiota can directly influence this disease and have shown that the intestinal microbiota of people with type 2 diabetes can be linked to a different metabolism of the amino acid histidine, which derives mainly from the diet. This amino acid, in turn, leads to the formation of imidazole propionic acid, a substance that alters the ability of cells to respond to insulin. Reducing the amount of imidazole propionate produced by bacteria could therefore be a new way of treating patients with type 2 diabetes. This substance does not cause all types of type 2 diabetes, but a hypothesis is that there are subpopulations of type 2 diabetes patients who may benefit from changing their diet or altering their gut microbiota to reduce imidazole propionate levels [143]. The researchers identified a high concentration of the substance imidazole propionate in patients with type 2 diabetes. Using fecal samples, it was also possible to show that the microbiota of people with type 2 diabetes produced imidazole propionate when histidine was added. This mechanism was not found in control subjects without diabetes. Gram negative bacteria, such as Bacteroides, contain large amounts of lipopolysaccharide (LPS), a strong activator of TLR4 (Toll like receptor 4) receptors, expressed in many somatic and CNS cells as well as on macrophages. The link between LPS and TLR4 triggers an inflammatory response and the expression and secretion of cytokines. In obese subjects, the circulating levels of LPS are very high and this increase is directly related to the increase in intestinal permeability due to a decrease in intestinal "tight junctions". LPS are carried by chylomicrons into the circulation. The increase in LPS is one of the factors that induces inflammation, as already mentioned, as well as insulin resistance, glucose intolerance and

obesity. The microbiota can also affect the absorption of monosaccharides. Some bacterial strains can induce a greater expression of SGLT-1 at the ileal level, while other strains can induce an increase in the expression of GLUT-2 at the level of the jejunum and ileum.

2.17 Microbiota and type 1 diabetes mellitus

The incidence of type 1 diabetes mellitus (DMT1) has been growing in all industrialized countries since the end of the second world war. This increase cannot be explained by the genetic aspect alone. In fact, migrant children from a population with a low risk of developing DMT1 assume the same risk as high-risk populations. Viruses certainly appear to be involved in the development of DMT1, but the cause and effect relationship between infection and disease has not yet been established. As already mentioned, the use of antibiotics also causes long-term changes and the western diet, high in fat, high in simple carbohydrates and low in fiber, can induce substantial functional changes in the intestinal microbiota. These data suggest that children without DMT1 may have had a more balanced and stable microbiota than children who developed DMT1 [145].

2.18 Microbiota and obesity

A clear example of the relationship between intestinal microbiota and metabolic diseases is offered to us by obesity which is a multifactorial pathology deriving from the interaction of individual genetics with the environment with a prevalence in the world that is increasing more and more markedly starting from the 70s-80s. Especially the increasingly affordable food, by facile availability, high energy density and poor quality and excess nutrition are among the most relevant causes in determining a significant increase in obesity. The same factors also have a considerable

importance in alteration of the microbiota. Although obesity and metabolic diseases have always been considered nutrition-related disorders, recent evidence shows that the intestinal microbiota plays an important role in the development of this metabolic disease. Recent studies have suggested that the microbiota of obese people may help the body increasing the energy extracted from food, suggesting that certain components of the gut microbiota may increase the likelihood of becoming obese. Although much of the research is still at the beginning, however, studies have revealed that obese people have a different composition of gut bacteria compared to lean individuals. In 2006, one of the first studies confirmed the relationship between microbiota, weight gain and obesity, a relationship determined by the ability of the microbiota to make a greater amount of assimilable energy available to the host. The study showed that microbiota transplantation from genetically obese mice with the *ob/ob* genotype into germ-free mice caused weight gain; this increase was not evident when the microbiota of non-obese mice was transplanted, with the same food intake. Studies on homozygous twins discordant for weight have helped to determine the correlation between microbiota, weight and nutrition. Subjects with obese phenotype and with lower bacterial richness have a reduction in the bacteria that produce butyrate, a lower production of methane and hydrogen, an increase in oxidative stress, which resulted in a greater tendency to develop inflammatory pictures. The intestinal microbiota influences the host's metabolism through various mechanisms including: the extraction of energy from some nutrients, the modulation of lipid metabolism, the alteration of endocrine functions and the increase in the inflammatory level. Obesity has been associated with an altered intestinal microbiota

characterized by high levels of Firmicutes and low levels of Bacteroides. The Western diet (high content of saturated fats, low presence of fibers, etc.) induces a reduction of Bacteroidetes strains and favors the development of Firmicutes strains, involved in the metabolism of carbohydrates. The microbiota of obese subjects has a prevalence of Firmicutes, while the microbiota of lean subjects has a prevalence of Bacteroidetes with a high Bacteroidetes/Firmicutes ratio. One of the most important bacterial strains in the prevention of obesity is *Akkermansia muciniphila* [145], which belongs to the *Verrucomicrobia* group. Many studies describe an inverse correlation between *Akkermansia muciniphila* concentration and genetic and dietary obesity patterns. The administration of prebiotics, dietary fibers such as inulin and its derivatives, induces a marked increase in *Akkermansia* in genetically obese mice, with an improvement in metabolic functions and glucose metabolism [146]. The microbiota influences the fermentation of indigestible carbohydrates into short-chain fatty acids (SCFA: butyric acid, acetic acid, and propionic acid). Butyric and propionic acid have an anti-obesogenic effect while acetic acid has the opposite effect. In fact, the first two are mainly produced by Bacteroidetes while the third by Firmicutes. Butyric acid stimulates the re-release of GLP-1 and GIP by L cells, improving insulin sensitivity. Propionic acid has positive effects on the inhibition of the functioning of Acetyl-CoA synthetase and therefore an effect on the synthesis of cholesterol. Acetic acid, on the other hand, is a substrate for lipogenesis and for the synthesis of cholesterol.

2.19 Microbiota and modulation strategies

Prebiotics are defined as fermentable carbohydrates but not digestible by humans capable of influencing

the intestinal microbiota in order to induce a health benefit to the host. The demonstrated benefits include an improvement in the insulin signal and its production. Among the prebiotics we find inulin, resistant starches and oligosaccharides. The use of prebiotics is able to modulate the development of many bacterial strains and, in particular, of Bacteroidetes to the detriment of Firmicutes, thus favoring a relationship between bacterial strains such as that found in the microbiota of lean subjects. Further-more, prebiotics have been shown to improve many metabolic parameters such as fasting blood glucose levels, glucose tolerance, reduction of plasma triglyceride levels, lipid infiltration of muscles, fat tissue mass, oxidative stress and to improve leptin sensitivity. Prebiotics also modulate the secretion of GLP-1 and GLP-2, and increase the feeling of satiety, with effects on appetite and the glucose response after a meal. Probiotics are living microorganisms that can improve the health of the host by modifying the microbiota. *Lactobacillus casei* induces a decrease in glycemic levels in mice with type 1 diabetes and prevents the onset of type 2 diabetes in mouse models. Administration of probiotics has been shown to reduce β -cell destruction, reduce oxidative damage to the pancreas, exhibit anti-inflammatory properties, reduce bacterial translocation between the gut and host, and reduce the expression of pro-inflammatory cytokines [148-150].

3. Conclusions

Cross-sectional and prospective studies indicate that postprandial hyperlipidemia, even in the presence of normal levels fasting lipid, is associated with an increased cardiovascular risk. It is observed more frequently in the conditions characterizing the multimetabolic syndrome, that is, in the presence of fasting hypertriglyceridemia, type 2 diabetes

mellitus, obesity and arterial hypertension. Insulin resistance in the liver and adipose tissue appears to be the common mechanism responsible for postprandial hyper-lipidemia in these conditions, all characterized by a high cardiovascular risk. Postprandial physical exercise is able to reduce the extent of postprandial lipemia. Lipid-lowering drugs, statins and in particular fibrates, are able to reduce postprandial lipemia. There is a lack of prospective studies on the relationship between postprandial lipemia and the incidence of cardiovascular events, as well as studies on the effect of correcting postprandial hyperlipidemia on cardiovascular risk. Numerous researches on the human intestinal microbiota show that the diet can act as a modulator of the composition and function of this microbial community in humans and animals. In conclusion, the changes in the microbiota that we find in obesity, metabolic syndrome, type 1 and type 2 diabetes could represent a potential therapeutic target: the use of predominantly local-acting therapies, with systemic effects, could become a new perspective of intervention. positive on the correlation of intestinal microbiota and metabolic diseases. It is evident that the mechanisms through which the microbiota regulates the host's metabolism are very complex and in the future, probably, new metabolic pathways will be identified. It is clear that if we feed our microbiota by optimizing the diet, reducing the use of antibiotics and recovering contact with the products that nature offers us, we will improve the well-being of this microbial community and therefore our health state. On this basis, the modification of the intestinal microecosystem can be taken as a key goal to achieve prophylactic or therapeutic effects in altered metabolic conditions and in inflammatory states. Using this knowledge to our advantage could help us stay healthy longer. In this way, fundamental ideas

are also provided for the development of new foods and food models that aim at optimizing the microbial activities in our intestine for an adequate exploitation of this enormous resource that every human being possesses. Our nutrition message must therefore continue to be to increase the consumption of complex carbohydrates that have a beneficial effect on our microbiota. Considering that the diet of the modern world has negatively changed our microbiota, we should therefore really rethink our way of eating and living, putting the well-being of the intestine among our priorities. Certainly there are still many gaps in our understanding of the interactions between diet and lifestyle, microbes and health and therefore the relationship between gut microbiota and metabolic diseases so that one day we may perhaps know exactly how to direct our diet in order to be able to "shape" our microbiota to improve our health. Therefore, we can revise the old aphorism of the philosopher Fierbach, arguing that we are not directly what we eat or what our mother eats, but we are what our microbiota eats and how the collective composition of our microbiota is modified by the diet. At present we haven't understood everything about the relationship between intestinal microbiota and metabolic diseases but we are certainly aware that many human diseases can be treated through the microbiota. Therefore, the fascination of this great scientific challenge remains, which will certainly open up new scenarios in the near future and perhaps will be able to give great answers that will allow us, in all probability, to write important pages in the history of medicine in the coming years [15].

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